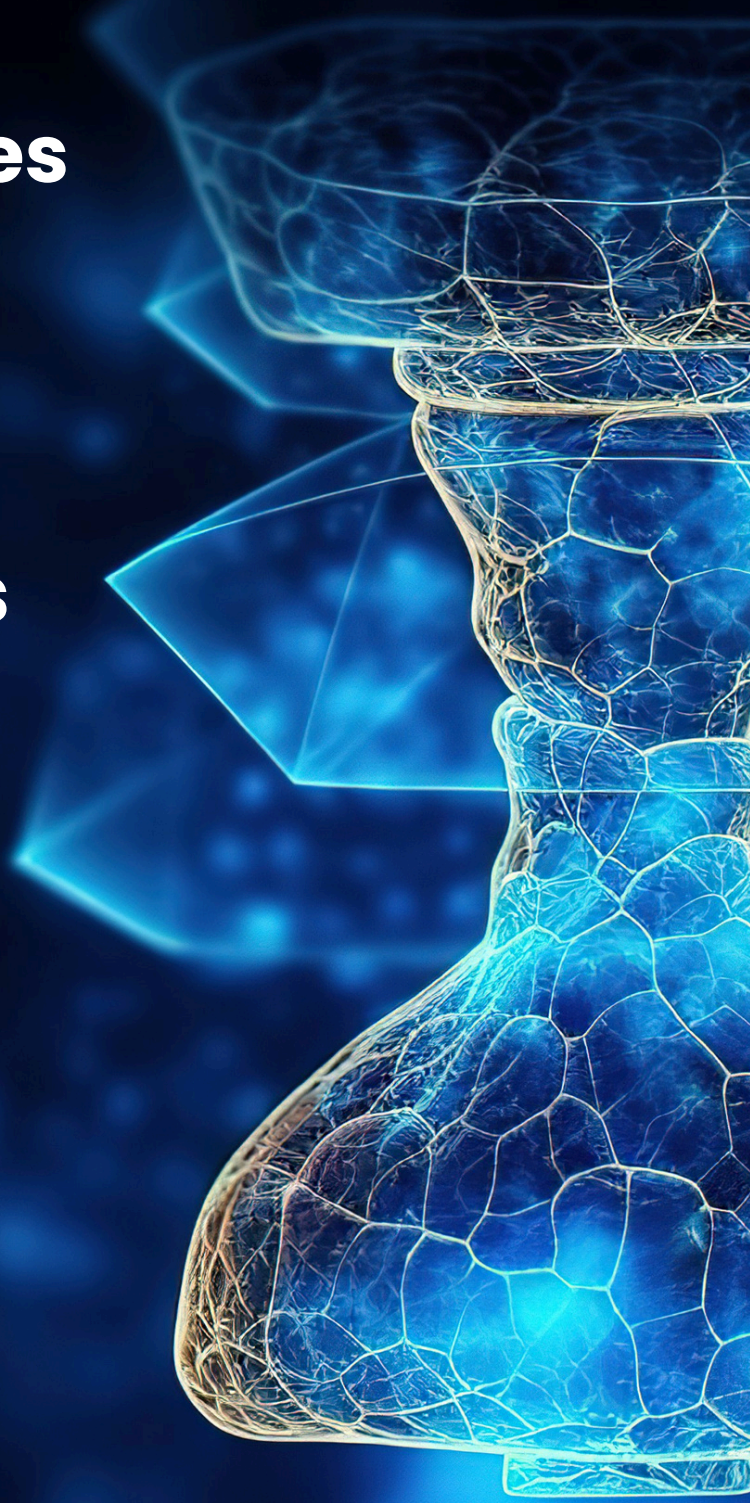
September 20th, 2024
9:00–17:00

Current challenges in the diagnosis and treatment of selected endocrinopathies



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9:00 Opening remarks

- Magdalena Sajdak, PhD – Polish Academy of Sciences Scientific Center in Paris
- Prof. Artur Bossowski – Medical University of Bialystok
- Prof. Jean-Claude Carel – Université Paris Cité, Hôpital Robert-Debré

9:15 Thyroid diseases and growth hormone therapy

- Prof. Jean-Claude Carel – Université Paris Cité, Hôpital Robert-Debré, France
  Growth hormone safety: the SAGhE study and beyond
- Dr Alicja Korpysz, PhD – The Children Memorial Health Institute, Warsaw, Poland
  Congenital growth deficiency. Effectiveness of GH therapy in SGA patients in the light of own experience
- Prof. Małgorzata Waśniewska MD, PhD – Medical University in Messina, Italy
  Selected clinical aspects including neoplastic changes in Hashimoto's thyroiditis
- Prof. Iwona Beń-Skowronek MD, PhD – Department of Pediatric Endocrinology and Diabetology, Lublin Medical University, Poland
  Polish recommendation for differentiated thyroid cancer in children and adolescent

10:55 Coffee break

11:15 Diabetes type 1 and immunogenetics

- Prof. Artur Bossowski MD, PhD – Medical University in Białystok, Poland
  Prospects of population screening test for type 1 DM in Poland and in the world
- Prof. Simon Fillatreau – Director of the Department of Immunology, Infectiology, and Hematology Institut Necker Enfants Malades, Paris, France
  Regulatory T cells in type 1 diabetes: characterization and therapeutic perspectives
- Prof. Piotr Trzonkowski MD, PhD – Head of Department of Immunology and Translantology, Gdanski Medical University, Poland
  From bench to bedside – T regulatory cells in the treatment of type 1 diabetes
- Prof. Jacques Beltrand – Université Paris Cité, Hôpital Necker-Enfants, France
  Innate immunity in type 1 diabetes
- Prof. Alfonso Galderisi – Yale University
  Beta cell function in type 1 diabetes

13:15 Poster session

Moderators:

- Prof. Barbara Głowińska-Olszewska MD, PhD
- Hanna Borysewicz-Sańczyk, PhD

Lunch break

Agenda

14:55 Varia

- Prof. Laetitia Martinerie – Université Paris Cité, Hôpital Robert-Debré, France
  Mineralocorticoid regulation in the fœtus and neonate – Implications for perinatal adaptations
- Prof. Catherine Chaussain
  Management of hypophosphatemia – X linked and beyond
- Prof. Nicolas de Roux – Université Paris Cité, Hôpital Robert-Debré, France
  Insights into gonadotropic axis regulation: lessons from rare diseases of pubertal development
- Prof. Mariusz Ratajczak MD, PhD – Medical University in Louisville, USA (online)
  Development early very small embryonic like stem cells (VSELs) are kept quiescent in adult tissues due to decrease in sensitivity to somatotrophic signaling

17:00 Closing remarks

- Magdalena Sajdak, PhD – Polish Academy of Sciences Scientific Center in Paris
- Prof. Artur Bossowski – Medical University of Bialystok
- Prof. Jean-Claude Carel – Université Paris Cité, Hôpital Robert-Debré

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- Magdalena Sajdak, PhD, Polish Academy of Sciences Scientific Center in Paris
- Karolina Siekierka, Polish Academy of Sciences Scientific Center in Paris

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- Prof. Iwona Beń-Skowronek
- Prof. Artur Bossowski
- Prof. Jean-Claude Carel
- Prof. Simon Fillatreau
- Prof. Alfonso Galderisi
- Dr Alicja Korpysz
- Prof. Laetitia Martinerie
- Prof. Mariusz Ratajczak
- Prof. Nicolas de Roux
- Prof. Piotr Trzonkowski
- Prof. Małgorzata Waśniewska

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- Mateusz Gliwiński
- Milena Jamiołkowska-Sztabkowska
- Elżbieta Parchanowicz
- Giorgia Pepe, PhD
- Magdalena Piotrowska-Mieczkowska, PhD
- Justyna Sakowska
- Magdalena Skorupska
- Karolina Stożek
- Zuzanna Wantoluk

1.

THROID DISEASES AND GROWTH HORMONE THERAPY

Growth hormone safety: the SAGhE study and beyond

Prof. Jean-Claude Carel – Université Paris Cité, Hôpital Universitaire Robert-Debré, France

Short-term and long-term safety are key concerns when using growth hormone to replace deficient hormone levels or to promote growth in short children. The history of pediatric endocrinology and the use of growth hormone are closely intertwined, with safety issues being perceived as a potential threat to this widely used treatment and, more broadly, to the professional community.

In 2006, following several safety signals, we initiated a large data collection effort, initially in France and later extended to several European countries, to gather information on the health status of adults who had been treated with recombinant growth hormone during childhood. This initiative allowed us to accumulate a substantial amount of data, covering more than 24,000 patients and over 400,000 patient-years, across several outcomes.

One of the key questions that emerged during the analysis was related to the classification of patients and their intrinsic risk of morbidity. This is evident when analyzing data from cancer survivors who have undergone multiple high-risk treatments known to have long-term effects. However, it is less straightforward when dealing with populations that may only differ slightly from the general population.

We will summarize the main findings from various published studies and discuss potential future developments to further address this critical issue.

Congenital growth deficiency. Effectiveness of GH therapy in SGA patients in the light of own experience

Dr Alicja Korpysz, PhD, "The Children Memorial Health" Institute, Warsaw, Poland

Introduction

IUGR (Intrauterine Growth Retardation) most often belong to GH (growth hormone) resistant, IGF1 resistant, rarely GH deficiency and genetically determined syndromes.
Growth hormone therapy is given to children born as SGA (Small for Gestation Age) and have growth deficiency. The initial trials were conducted at the end of the last century. In Poland, this therapy has been administered since 2015. Many world reports confirmed that the effectiveness of therapies is determined by the severity of hypotrophies, parental height, severity of growth deficiency, timing of treatment initiation, dose of growth hormone, duration of therapy, bone age and concomitant diseases.

Study 1

Aim: The objective of our study was to estimate the parameters mentioned above for a group of SGA children who were treated with growth hormone throughout the year and later as well.

Material and methods: 40 SGA children at 8.2 years, at 36 HBD with weight of 1802g (-3 SD) and birth length of 44.4 cm (-1.2 SD). Parental height was: father 173.2 cm (-1.1 SD) and mother 159.8 cm (-0.9 SD). Bone age was estimated at 6.1 years.The duration of growth hormone therapy was 4.6 years. The patients with height deficiency of 115.49 cm (-2.6 SD) were subjected to one year growth hormone therapy at the dose of V1-0.26, V2-0.27 and V3-0.29 mg/kg/week. The final dose was 0.35 mg/kg/week at the age of 12.8 years. Pre-treatment height was assessed at V1, after 6 months (V2), 12 months (V3) and later on.The relationship of response to treatment was estimated according to birth weight, parental height, dose of treatment, time of therapy initiation, degree of growth deficiency, and bone age.

Results: One year's therapy resulted in a significant improvement in height from 115.49 cm (-2.69 SD) -V1 to 118.46cm (-2.38 SD) after 6 months -V2 and 123.14cm (-2 SD) after a year -V3; p=0.02 (V1-V2cm); p=0.00000 (V1-V3 cm); p= 0.01 (V1-V2 SD), p=0.00000 (V1-V3 SD). The final growth of 40 patients after 4.6 years of treatment averaged **115.49 cm** (V1) to **149.56 cm** (VF), p=0.00000000; **-2.53 SD** to **-1.2 SD**, p=0.000000.After 6 months of therapy (V2), there was a significant correlation between HT and the height deficiency (V1 cm/SD) (p= 0.00000 and p= 0.0018 respectively), bone age (p=0.00000), time of therapy initiation (p=0.00000). After 12 months of GHT (V3), the significant correlation was found between HT and height deficiency (V1 cm/SD) (p=0.000000; p=0.0019 respectively), bone age (p=0.000000), time of therapy (p=0.000000) as well. The final height correlated with height deficiency (cm/SD) (p=0.00000; p=0.038), bone age (p= 0.0028) and time of therapy initiation (p=0.00001).

Conclusion: Growth hormone therapy is an absolute necessity for SGA children with growth deficiency. The effectiveness of these therapies in the study group demonstrates a significant dependence on baseline growth deficiency, bone age and start-up time.

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Study 2

Aim: The attemp of assessment the markers of bone formation and bone resorption for SGA children during growth hormone treatment.

Material and methods: 25 SGA children at 7.8 ± 1.8 years, born at 36.4 ± 4.11 Hbd with birth weight : 1776 ± 699g (-3,3SD) and birt length: 44.9 ± 6.9cm (-1,2SD). The height deficiency was 111.8 ± 10.3 cm (-2.7SD). Growth hormone therapy was conducted during a year with the dose of 0,24mg/kg/week. The bone formation and bone resorption: Ctx, P1NP, NT-proCNP, PIIINP were estimated after 6 and 12 months of the GHT.

Results: A significant increase in bone resorption markers **Ctx** (ng/ml) was obtained both after 6 and 12 months, respectively (1.7 vs 2.4 p=0.000) and (1.7 vs 2.3 p=0.000). **P1NP** (ng/ml) bone markers increase at 6 months (592 vs 840 p=0.000) and after 12 months therapy (592 vs 804 p=0.000). The **P3NP** (ug/ml) marker of collagen synthesis also increased after 12 months of therapy (13 vs 14.8 p=0.000). We have obtained significant correlation beetween height (cm) and Ctx after 6 months (r=0.4, p=0.04) (d v1- v3 Ctx /height (cm)=0.4; d v1-v3 Ctx/height (SD) =0.5) as well height (SD) :r=0,15, p=0,05. P1NP / height (SD) after 12 months (r=0.44, p=0.025) (d v1-v3 P1NP/height (SD) =0.49).

Conclusion: A strong reaction of bone resorption and bone formation markers indices during growth hormone therapy may determine their selection as an initial prediction of those treatment.

Future

We want to estimate GHT for SGA chldren according to congenital growth deficiency several groups:

1. The growth hormone signal transmission : GH resistant (5p13-12); IGF1 deficiency (12q 22-24.1), IGF1 resistance (15q 25-26),IGF2 deficiency (11p15.5), STAT5b deficiency (17q 11.2), ALS deficiency (16p13.3),PAPP2 deficiency (1q25.2);
2. Gene SHOX anomalies:Turner Syndrome(Xp-22-23),Dyshondrostenosis Leri -Weilla (Xp22-32, Yp11.2);
3. Achondroplasia, hipochondroplasia, gene FGFR3 (4p16.3);
4. Syndromes dictated by uniparental disomy: Silver Russel Syndrome (7p11.2, ICR loss of metylation 11p15.5, CDKN1C, HMGA2- PLAG1-IGF2), Prader Willi Syndrome (maternal disomy15p12), Templ Syndrome (maternal disomy 14p);
5. Syndromes aassociated with RAS/MAPK signal: Noonan Syndrome (PTPN 12q24.1);
6. Syndromes concerning microcephalie: 3M Syndrome (CUL7, 6q21.2, OBSL1, CCDC8-19q13.3),Secel Syndrome (SCKL1 3q22-24, SCKL2 18p11.31-q11.2, SCKL3 14q21-22),Meier- Gorlin Syndrome (CDC6 17q27, CDT1 16q24, ORC1 1p32), Bloom Syndrome (BLM 15q26.1), Down Syndrome (trisomy 21),Grouchy Syndrome (18q 21-23); 7.ISS (Idiopatic Short Stature).

The same was true for calculations in SD: V2 HT SD associated with height deficiency (V1cm/ SD) (p=0.0009, p=0.00000), time of therapy initiation (p=0.03); V3 HT SD also associated with height deficiency (V1cm/SD) (p=0.0006, p=0.00000) and time of therapy initiation (p=0.023).
Final HT SD related to the height deficiency (V1SD) p=0.0001.

Conclusion

Growth hormone therapy is an absolute necessity for SGA children with growth deficiency. The effectiveness of these therapies in the study group demonstrates a significant dependence on baseline growth deficiency, bone age and start-up time.

Selected clinical aspects including neoplastic changes in Hashimoto's thyroiditis

Prof. Małgorzata Waśniewska MD, PhD; mwasniewska@unime.it
Department of Human Pathology of Adulthood and Childhood
University of Messina, Italy

Each thyroid nodule in a child must be examined with a more timely and accurate diagnostic approach than in an adult, due to the greater frequency with which malignant neoplastic transformation occurs. The relative risk of malignant neoplasia of a nodule is much higher in children (19 -26.4%) than in adults (5-10%).

Accumulating data suggest that patients with a nodule and thyrotropin (TSH) levels in the upper centiles of the reference range might be at increased risk for possible neoplastic evolution of nodules with malignancy.

It has been also hypothesized that Hashimoto's thyroiditis (HT) is associated with an increased risk of papillary thyroid carcinoma (PTC). Despite numerous studies that have evaluated the association between HT and TC, no significant results are available, and the relationship remains controversial. HT could be associated with an increased risk of TC according to the "inflammation-tumorigenesis" theory. Wide variability in the prevalence of the association between HT and TC (up to 85%).

PTCs, in the context of HT, are significantly correlated with female sex, multifocal involvement, absence of extrathyroidal extension and lymph node metastases.

The association between HT and TC may also be mediated by a persistent increase in serum TSH levels, both in the context of subclinical hypothyroidism and in overt hypothyroidism (possible overstimulation of follicular cell proliferation and growth).

Current guidelines suggest performing an ultrasound in children with autoimmune thyroiditis in the presence of a palpable nodule, asymmetry of the gland and cervical lymphadenopathy on examination.

The personal experience on that topic will be presented.

Polish recommendation for differentiated thyroid cancer in children and adolescent

Prof. Iwona Beń-Skowronek MD, PhD
Dept. Pediatric Endocrinology and Diabetology,
Medical University of Lublin, Poland

The annual incidence of thyroid cancers is 4.8 to 5.9 cases per 1 million people aged 0 to 19 years, accounting for approximately 1.5% of all cancers in this age group. The management of thyroid cancers recently has become far more nuanced. With specifically tailored treatments becoming commonplace, it is important to consider each patient individually.

Additionally, it is important to note that while a number of different groups have put forth guidelines for the management of thyroid surveillance and cancer therapy. With the widespread use of sensitive imaging techniques, which include neck visualization, a conspicuous number of thyroid nodules emerge and demand attention. In the case of cancer diagnosis, most are small, intrathyroidal and indolent neoplasms that can safely be managed conservatively. Differentiated thyroid cancers (DTC) is a rare cancer in children and adolescents, having features of different clinical presentation, biological behavior, and treatment from adult population. Most of the patient management guidelines are based on literature on adult population and the literature on children and adolescents still limited. There are still unsettled issues regarding both patient management and the therapy. However, the current approach for treatment of DTC includes thyroidectomy, lymph node dissection in patients with nodal metastases and possible use of Iodine-131 radiotherapy. Thus, the present guidelines aim at providing a clinical practice guide for the initial workup and the subsequent management of children harboring DTC. The polish DTC guidelines were prepared on base ATA and ETA guidelines by expert working group. According the guidelines ultrasound of thyroid and FNAB is the gold standard of diagnosis, but elastography should be used for pick of nodule for FNAB. The molecular diagnostic methods of FNAB and genetical markers may be usefull for qualification for surgery patients with uncertain histological diagnosis. The thyroidectomy is method of choice for DTC treatment, but radioiodine therapy may by reserved only for DTC with high risk.

In conclusion : the DTC diagnosis and treatment should be personalised.

2.

DIABETES TYPE 1 AND IMMUNOGENETICS

Prospects of population screening test for type 1 DM in Poland and in the word

Prof. Artur Bossowski MD, PhD
Head of Department od Pediatric, Endocrinology and Diabetes, with a Cardiology Unit, Medical University in Białystok, Poland

Type 1 diabetes (T1D) is the most frequent chronic autoimmune disease in childhood and adolescence, its incidence is increasing particularly in preschool children, and up to 30- 60% of young patients present with diabetic ketoacidosis (DKA), a severe and life-threatening complication. The majority of screening efforts have been performed in the at-risk group, i.e., relatives of people with T1D; but around 80-90% of young patients who eventually develop T1D do not have a family history. Some studies in Europe and the USA have clearly shown that a public health screening of children (with positive autoantibodies) is effective in reducing the prevalence of DKA by more than 10 times, decreasing the rate of hospitalization and its costs, providing psychological, emotional, and social support to children and their families.

The population study of early detection of T1D in asymptomatic children in the North-Eastern region of Poland is an extension of the Pre-d1abetes Study conducted by our clinic between 2019 and 2023 in collaboration with 14 Polish diabetes centres. A total of 1288 patients aged between 7 months and 18 years were studied with positive family of T1D. Positive 3-screen ELISA values were observed in 112 patients (8.69%). During analysis of individual antibody types, 76 children with multiple (two or more) antibodies were identified, constituting a pre-diabetes group (5.9%). In second step we identify high-risk patients for development of T1D among general population healthy pre-school and primary school children age 1-9 years in North-Eastern of Poland. A 3 screen RSR ELISA (Cardiff, UK) was used. In cases of a positive screen, were analysed specific antibodies: anti-GAD, anti-ZnT8, anti-IA2 and IAA (anti-insulin) by ELISA and RIA methods. Nine regions of Podlaskie voivodeship were selected for the pilot study. 3.352 children were screened, with a positive result in 208 (6.18%) of subjects. In addition, 0.53% had two and 0.69% two or more antibodies, giving the highest risk of developing DT1 among the tested children. Positive results of the study will allow for appropriate education of families to early symptoms of T1D, implementation of diets with a low glycemic index, regular physical activity and the inclusion of the children to Diabetes Clinic for follow-up. The research was the first in Poland and unique in Europe.

In summary, a population studies using the 3 Screen ELISA (RSR Ltd) test can recognize pre-clinical T1D before development of carbohydrate abnormalities. Patient follow up with early education and multidirectional diabetes care should prevent occurrence of ketoacidosis associated with severe clinical manifestations. This opens the possibility of therapeutic interventions in innovative clinical programs.

Regulatory T cells in type 1 diabetes: characterization and therapeutic perspectives

Prof. Simon Fillatreau, Institut Necker Enfants Malades (INEM), Paris, France, on behalf of the ARTiDe consortium

Type 1 diabetes (T1D) is among the most frequent chronic immune-mediated inflammatory diseases in children. Although the immune system is recognized as the chief driver of the disease, there is currently no therapy to cure T1D by intercepting the deleterious immune response. Consequently, patients are currently treated for life by insulin replacement therapy, which only addresses the symptoms of the disease. In the last years, the knowledge of the immune mechanisms underpinning T1D development has remarkably improved, which has opened the way for the development of new generation of immunotherapies more specifically targeting the drivers of the disease than previously available drugs to achieve more effective and safer effects. In particular, genetic studies have underlined the strong association between the risk of developing T1D and polymorphisms in Human leukocyte Antigen class II antigens that govern CD4+ T cell immunity, and treatment with the pan T cell-targeting antibody anti-CD3 delayed disease onset in at risk individuals. Thus, an optimal therapy should specifically remove the disease-relevant autoreactive T cell compartment while maintaining intact immunity against infectious agents and tumors. CD4+Foxp3+ T regulatory cells (Tregs) represent an ideal cell type to achieve this goal as they are normally in charge of maintaining tolerance to self antigens, and they appear to be defective in T1D. There is thus a great interest to develop antigen-specific Tregs for cell therapy in T1D and other IMIDs. However, several challenges must be overcome to bring autoreactive Tregs to the clinic, including the knowledge of the epitopes recognized by protective Tregs in T1D, the identification of the optimal TCR to produce protective Tregs by TCR gene transfer, the pre-clinical validation of such TCR-engineered Tregs, and a technology to produce human genetically modified Tregs in a format suitable for application in patients. The European project "autoantigen-specific regulatory T cell therapy against type 1 diabetes (ARTiDe; https://artide.eu) ambitions to overcome all these challenges and to be in the position to start a phase I clinical trials in around 5 years. During this presentation, I will present the rationale for developing autoreactive Tregs for cell therapy in T1D, provide some initial information on the progress of our work for the characterization of autoreactive Tregs in T1D, and highlight our path to reach the clinic.

From bench to bedside - T regulatory cells in the treatment of type 1 diabetes

Prof. Piotr Trzonkowski MD, PhD
Department of Medical Immunology, Medical University of Gdańsk, Poland;
Poltreg S.A. Gdańsk

T regulatory cells (Tregs) are considered a viable option in immunosuppressive treatment in the clinic. First promising clinical experiments and trials with clinical-grade Tregs cultured as advanced therapy medicinal product (ATMP) are completed already. In our centre, the drug has been tested in graft versus host disease, type 1 diabetes and multiple sclerosis. We will present the path from preclinical studies to the results of clinical trials and future perspectives on the application of this cellular drug in the treatment and prophylaxis of type 1 diabetes.

Innate immunity in type 1 diabetes

Prof. Jacques Beltrand, Leo Bertrand, Adrien Caffiers, Lucie Beaudoin, Agnès Lehuen
Hôpital Necker Enfants Malades, Université Paris Cîté, Institut Cochin

Type 1 diabetes (T1D) is an autoimmune disease characterized by the selective destruction of pancreatic β cells by the immune system. The resulting hyperglycemia requires patients to follow a lifelong insulin replacement therapy, and despite treatment patients remain vulnera- ble to multiple disease complications. Studies in human patients and animal models of the dis- ease have demonstrated that, while β-cell destruction requires the cytotoxic activity of adap- tive T cells, innate immune cells are involved during all stages of pathogenesis. Whereas these cells are very diverse in shape and functions, they all share common properties, including a spontaneous reactivity to signals of microbial invasion and tissue damage, a rapid response to such stimuli, and the ability to support adaptive immune responses by priming and release of appropriate cytokines. Therefore, understanding why and how innate immunity is involved in T1D pathogenesis is essential to com- prehend its onset, particularly with regard to known genetic and environmental risk factors of T1D. iNKT and MAIT cells are innate-like T cells sharing many characteristics. These include a restricted TCR repertoire, made of an invariant TCR-alpha chain, recognition of non-protein antigens presented by the nonpolymorphic class Ib molecules CD1d and MR1, and an effector memory phenotype. These innate-like T cells are conserved in mammals and are abundant in blood and tissues such as the liver, mucosa and skin. These cells can respond rapidly through TCR activation and inflammatory cytokines thereby stimulating immune response against infectious pathogens as well as participating to tissue homeostasis. Studies in patients and mouse models have revealed their ambivalent roles in the pathogenesis of type 1 diabetes and being either protective or deleterious in various autoimmune, metabolic and infectious diseases. We will describe the direct immune effector functions of innate immunity in the pancreatic islets during T1D, before de- scribing how innate cells are critical in modulating the autoimmune and tolerogenic adaptive immune responses against β cells. Finally, we discuss how innate immune reactions at locations distant from the pancreas, such as the gut, may contribute to disease progression.

Beta cell function in (preclinical) Type 1 diabetes.

Prof. Alfonso Galderisi
Yale University

Presymptomatic type 1 diabetes (T1D) is featured by complex metabolic changes, that includes not only a declining insulin secretion but also variable changes in insulin sensitivity and clearance. The use of metrics that account for both insulin secretion and sensitivity is of key relevance in pediatric studies due to the physiological changes of insulin sensitivity across the ages and the adaptive response of insulin secretion.

Relying on the so called “metabolic modelling” we will revise the measurable changes of the metabolic phenotype in pivotal trials conducted in Stage 1 or Stage 2 T1D, the relationship between the metabo- and immuno-phenotype during clinical trials and the relevance of metabolic endpoints as predictors of disease progression and early treatment response.

Metabolic-modelling will be adopted to describe the heterogeneity of the current T1D stages and its implication in the design of clinical trials.

3.

VARIA

Hormonal regulation of sodium homeostasis in the perinatal period

Prof. Laetitia Martinerie
Service d'endocrinologie Pédiatrique. Centre de Référence Maladies Endocriniennes Rares de la Croissance et du Développement. Hôpital Universitaire Robert-Debré. Groupe Hospitalo-Universitaire de l'Assistance Publique-Hôpitaux de Paris Nord, Paris, France;
Université Paris Cité, Faculté de Santé, UFR de Médecine, Paris, France;
INSERM Physiologie et Physiopathologie Endocriniennes, Université Paris-Saclay, Le Kremlin-Bicêtre

The human kidney displays a tubular immaturity at birth, with sodium waste, responsible for a negative sodium balance, and an impaired ability to reabsorb water, which is aggravated under circumstances such as prematurity, pyelonephritis and gastroenteritis. This inability to maintain homeostatic functions is a major problem encountered by pediatricians, most notably in preterm infants. Indeed, the challenge is to find a balance between the lethal risk of dehydration and the associated morbidity of excessive hydro-mineral supplementation, contributing to severe complications such as intraventricular hemorrhage and bronchopulmonary dysplasia. A better understanding of water and sodium regulation in the neonatal period is a prerequisite in order to propose new therapeutic strategies for the management of preterm infants.

Sodium reabsorption is mainly controlled by aldosterone, a steroid hormone synthesized in the zona glomerulosa of the adrenal gland, secondary to renin stimulation via angiotensin II and to potassium stimulation. In the distal nephron, aldosterone, by binding to its receptor, the mineralocorticoid receptor, a transcription factor, tightly regulates the expression and the activity of several transport proteins implicated in sodium, potassium and water homeostasis, as the alpha subunit of the epithelial sodium channel, the Na-K-ATPase and the aquaporin 2.

We have demonstrated that neonatal sodium wasting is associated with a physiological renal aldosterone resistance in relation to a low renal mineralocorticoid receptor (MR) expression at birth in full-term infants, both in humans and mice, along with a down regulation of other mineralocorticoid signaling key-players. Moreover, very preterm infants present with defective aldosterone secretion while the kidney remains sensitive to aldosterone action during this period.

Thus, the neonatal period is characterized by defective mineralocorticoid signaling from two different mechanisms in preterm and full-term newborns. These results open new therapeutic possibilities for very preterm infants in order to prevent from sodium wasting.

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Insight into rare endocrine diseases through tooth exploration

Prof. Catherine Chaussain (DDS, PhD) Université Paris Cité,
Dental school and lab BRIO URP2496;
Bretonneau Hospital, APHP, Paris, France

Bones and teeth are the most important mineralized tissues in the body. They share several mechanisms related to their development and mineralization, including the signaling pathways that regulate the differentiation of their cell types 1, 2. Therefore, dental complications are a common morbidity in patients with endocrine disorders. Depending on the disorder, either the tooth structure, its morphology, or the number of teeth may be affected. In addition, malocclusions and craniofacial abnormalities such as craniosynostosis may also be present. Rare bone disorders related to the mineral homeostasis or affecting genes encoding a component of the extracellular matrix can dramatically affect tooth mineralization. As a consequence, patients may endure early tooth loss, or high susceptibility to caries, periodontitis or pulp infections1, 2,3. The aim of this presentation will be to highlight the dental aspects of rare endocrine diseases and the impact of their complications on the patient's quality of life. In addition, we will show how a thorough dental examination can support the diagnosis of a rare endocrine disorder, and how ultrastructural examination of the tooth can provide new insights into the pathophysiological mechanisms associated with the disorder. In addition, we will discuss how the ultrastructural examination of the tooth can reveal how a systemic treatment improves the mineralization process. Overall, this presentation will urge the need to include a dentist as part of the multidisciplinary team caring for the patient.

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Insights into gonadotropic axis regulation: lessons from rare diseases of pubertal development

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Since the discovery of the first Kallmann syndrome gene in 1991, many genes have been linked to isolated or syndromic hypogonadotropic hypogonadism. These studies have revealed the very high complexity of the genetic determinism of the gonadotropic deficiency with several modes of transmission. This strategy helped to make major advance in the understanding of puberty onset diseases but also paved the way for fundamental research to understand the development of the gonadotropic axis as well as in its neuroendocrine regulation. At the opposite side of the spectrum, the genetic of central precocious puberty represents a more complex question. Recent epidemiological studies of PPC revealed monogenic, polygenic but also multifactorial modes of transmission. In addition, the development of an in-vivo model of central precocious puberty in mice looks more challenging than previously thought which impedes the validation of candidate genes.

In this lecture, I will present past and recent examples of rare diseases with abnormal timing of puberty which has led to increase our knowledge on the gonadotropic axis development and physiology.

Development early very small embryonic like stem cells (VSELs) are kept quiescent in adult tissues due to decrease in sensitivity to somatotrophic signaling

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Regenerative medicine is searching for stem cells with the potential to differentiate into all three germ layers. Evidence accumulated that adult tissues harbor a population of very rare stem cells endowed with broad differentiation potential. These dormant, cells described as very small embryonic-like stem cells (VSELs) display several epiblast/germline markers what suggest their embryonic origin and developmental deposition in adult tissues. Recently, we found that VSELs do express several sex hormone (SexHs) receptors and respond in vivo to SexHs stimulation. Moreover, since VSELs share several markers characteristic of migrating primordial germ cells (PGCs) and can be specified into long-term hematopoietic hematopoietic stem cells (LT-HSCs) and mesenchymal stem cells (MSCs), this observation sheds new light on the BM stem cell hierarchy. Nevertheless, in spite of the expression of pluripotent stem cell markers, changes in the epigenetic signature of imprinted genes (e.g., by erasure of imprinting at the Igf-2–H19 locus) in VSELs are involved in their resistance to Igf-1/Igf-2 signaling and keep these cells in adult tissues in quiescent state. As reported in several emergency situations related to organ damage (e.g., heart infarct, stroke, skin burns), VSELs can be activated and mobilized into peripheral blood and in appropriate animal models contribute to tissue organ/regeneration. Interestingly, their number correlates with life span in mice and we noticed a positive effect of regular physical exercise and calorie restriction on ameliorating age-dependent depletion of VSELs from adult tissues. Recently, to bring these cells for potential clinical applications we developed an efficient ex vivo expansion strategy for these cells.

4.

POSTER SESSION

Application of Shear Wave Elastography (SWE) in the management of thyroid nodules in children and adolescents

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Background: Shear wave elastography (SWE) is an ultrasound diagnostic method used to measure tissue stiffness. Since the mechanical properties of tissue involved in the pathological process are changed, SWE might indicate regions of the examined tissue covered by the disease. It is well documented, that SWE helps to differentiate benign and malignant nodules in thyroid gland in adults, however there are still few studies on application of SWE in thyroid diagnosis in children. The purpose of the study was to assess the application of SWE based on Young's modulus expressed in kPa in the management of thyroid nodules in children and adolescents. Methods: 116 pediatric patients (81 girls and 35 boys) with 168 thyroid nodules were enrolled to the study and were qualified to SWE which followed fine needle aspiration biopsy. Results: According to the result of cytological examination presented in Bethesda system, nodules were qualified as benign (147 nodules with II category according to Bethesda system) and suspected (21 nodules with III, IV and V category according to Bethesda system). Benign cytological diagnosis were nodular goiter, parenchymal goiter, nodular colloid goiter or lymphocytic inflammation. Among suspected nodules 15 were diagnosed as III according to Bethesda system (AUS - Atypia of Undetermined Significance or FLUS - Follicular Lesion of Undetermined Significance in cytology), 1 nodule was diagnosed as IV according to Bethesda system (suspicious for follicular neoplasm - oxyphilic cell tumor) and 5 as V according to Bethesda system (suspicious for malignancy). There were no significant differences between TSH and fT4 concentration between benign and suspicious group. Patients with benign and suspected thyroid nodules were of comparable age. Mean SWE in benign nodules was statistically significant lower than in nodules with suspected cytology (42.22±16.69 vs. 57.4±24.0 kPa, p=0.0004). Moreover there was a significant correlation between the Bethesda scale and SWE values. 5 patients from suspicious group revealed to be malignant in final histopathological examination. Conclusion: Our results suggest that SWE is a viable diagnostic method, however it still seems to need some adjustment for pediatric patients.

Mechanisms Regulating T-Cell Dynamics in Type 1 Diabetes Mellitus: A Comparative Study of Newly Diagnosed and Long-Term Patients with and without Polyclonal Treg Therapy

Gliwiński M, Iwaszkiewicz-Grześ D, Wołoszyn-Durkiewicz A, Tarnowska M, Żalińska M, Hennig M, Zielińska H, Dukat-Mazurek A, Zielkowska-Dębska J, Zieliński M, Jaźwińska-Curyłło A, Owczuk R, Jarosz-Chobot P, Bossowski A, Szadkowska A, Młynarski W, Marek-Trzonkowska N, Moszkowska G, Siebert J, Myśliwiec M, Trzonkowski P.

Objective: This study aimed to uncover mechanisms that contribute to the progression of type 1 diabetes mellitus (T1DM), where pancreatic islets are destroyed by autoreactive T conventional cells (Tconvs) that are not sufficiently regulated by T regulatory cells (Tregs).

Research Design and Methods: We examined the T-cell compartments in patients newly diagnosed with T1DM (NDT1DM), those with long-term T1DM (LDT1DM), and LDT1DM patients treated with polyclonal Tregs. We also explored whether antigen specificity influenced the behavior of Tregs expanded for clinical use and their interaction with autologous sentinel Tconvs.

Results: Patients with LDT1DM showed T-cell changes similar to immunosenescence and an increase in specific vβ/T-cell receptor (TCR) clones in both Tconvs and Tregs. Treg treatment partially reversed these immunosenescence-like changes. LDT1DM patients had a higher percentage of proinsulin-specific T cells compared to GAD65-specific ones. Antigen-specific subsets were more prevalent in expanded cultures than in peripheral blood. Proinsulin-specific Tconvs proliferated more than Tregs, although some proinsulin-specific Tregs were exceptionally high at baseline and remained elevated in expanded clinical products compared to corresponding Tconvs in sentinel cultures.

Conclusions: T1DM is associated with immunosenescence-like T-cell changes and decreased diversity of T-cell clones. The similar expansion of TCR families in Tconvs and Tregs suggests a common autoantigen. Polyclonal Treg therapy partially mitigated these effects. Proinsulin-specific Tregs dominate the immune response in T1DM patients, likely leading to better control of autoreactive Tconvs.

Trial Registration Number: EudraCT 2014-004319-35.

Endothelial progenitor cells and circulating endothelial cells levels in children at type 1 diabetes onset

Milena Jamiolkowska-Sztabkowska, Kamil Grubczak, Aleksandra Starosz, Marcin Moniuszko, Artur Bossowski, Barbara Glowińska-Olszewska

Objectives: The aim of the study was to analyze endothelial progenitor cells (EPC) and circulating endothelial cells (CEC) at the time of type 1 diabetes (T1D) diagnosis in relation to patients' clinical state, remaining insulin secretion and partial remission (PR) occurrence.

Methods: We recruited 45 children admitted to hospital due to newly-diagnosed T1D, (mean age 10.8 yrs) and 20 healthy peers as a control group (mean age 13 yrs). EPC and CEC were assessed at disease onset in PBMC isolated from whole peripheral blood with the use of flow cytometry. Clinical data regarding patients's condition, C-peptide secretion and further PR prevalence were analyzed.

Results: T1D diagnosed patients presented higher EPC levels than control group (p=0.026), while there was no statistical difference in CEC levels and EPC/CEC ratio. Considering only T1D patients, children with better clinical condition presented lower EPC (p=0.021) and lower EPC/CEC ratio (p=0.0002). Patients with C-peptide secretion within normal range at disease onset also presented lower EPC/CEC ratio (p=0.027). Higher levels of EPC were observed more frequently in patients with higher glucose (p=0.025), decreased C-peptide (p=0.016) and lower stimulated C-peptide (p=0.033). Higher EPC were also observed more frequently among patients with olny one positive islet-autoantibody (p=0.022). Presence of DKA was related to higher EPC/CEC ratio (p=0.034). Statistically significant higher levels of CEC were observed only in patients who presented partial remission of the disease at 6 months after diagnosis (p=0.03). In the study group positive correlations of CEC with age, BMI at onset, and BMI in following years were observed. EPC/CEC ratio correlated positively with glucose level at hospital admisiion, and negatively with the age, BMI, pH and stimulated C-peptide level.

Conclusions: Hyperglycemia and DKA lead to EPC stimulation and EPC/CEC elevation, while CEC seem to be dependent on patient's age and nutrition. EPC's are elevated in patients with poor C-peptide secretion, but there is a need of more detailed investigation to establish the underlying mechanism.

Papillary thyroid cancer in children - case analysis

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Keywords: papillary thyroid cancer (PTC); children, thyroid ultrasonography; elastography; surgery; radioactive iodine (RAI)

Thyroid cancer is the most common malignant tumor of endocrine glands in children, accounting for about 2% of all developmental age cancers. In Poland, 40-50 new cases of thyroid cancer in children are reported annually (1-3:1,000,000). The most common type of thyroid cancer is papillary thyroid cancer. We present three cases of papillary thyroid cancer from the Department of Pediatrics, E**ndocrinology and Diabetology with the Cardiology Divisions of the Medical University of Białystok**

Case 1: A 15-year-old girl with a thyroid nodule had an ultrasound (US) showing hypoechoic areas in the left lobe (sized 6.4 x 5 x 6.4 mm and 6.7 x 5.2 x 12.8 mm with a hyperechoic part), with an elastography ROI1/ROI2 ratio of 2.7. Cytological examination indicated nodular goiter with single oxyphilic cells (Bethesda II/VI). A follow-up biopsy after a year revealed in a hypoechoic area with a halo in the left lobe (0.49 x 0.6 x 0.72 cm) - suspected follicular cancer (Bethesda IV/VI). A total thyroidectomy was performed, during which papillary thyroid cancer was diagnosed intraoperatively, and the procedure was extended by lymphadenectomy of the paratracheal and pretracheal lymph nodes. The treatment was supplemented with radioiodine therapy.

Case 2: A 15-year-old girl with Hashimoto's disease had a US revealing a hypoechoic lesion with increased flow in the left lobe (sized 3.7 x 2.4 x 4.3 mm) and reactive lymph nodes on the left side. Cytological examination indicated probable papillary cancer in the course of lymphocytic inflammation (Bethesda V/VI). A total thyroidectomy and central neck lymph node dissection were performed. Histopathological examination revealed multifocal papillary thyroid cancer in the left lobe and metastatic cells in the lymph nodes (pT1amN0R0). Additionally, radiotherapy was administered.

Case 3: The 16-year-old patient sought medical attention due to an abnormal thyroid US result. Imaging described a solid-cystic lesion in the left lobe (9 x 9 x 10 mm) with calcifications. Fine-needle aspiration biopsy suggested papillary thyroid cancer (Bethesda V/VI). The girl underwent total thyroidectomy with selective lymphadenectomy. The treatment was complemented with radiotherapy.

Conclusions: The diagnosis of thyroid cancers in children is based on thyroid ultrasound and fine-needle aspiration biopsy. Elastography may be also useful in the diagnostic process, as it non-invasively assesses the risk of malignancy of the lesions. Early diagnosis and precise evaluation of the nature of the lesions are crucial for the effective treatment of young patients.

Relationship between serum and faecal zonulin concentration and glucidic metabolism in children and adolescents with obesity

Presenting author: Giorgia Pepe

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BACKGROUND: due to the well-known association between intestinal permeability and obesity, zonulin has been recently proposed as an indicator of intestinal mucosal barrier integrity. Nevertheless, data about zonulin are extremely scarce in pediatric age.

OBJECTIVES: aim of this study was to investigate the relationship between serum and faecal zonulin levels with body mass index (BMI) and biochemical markers of insulin resistance (IR), insulin sensitivity, β-cell function and cardio-metabolic risk in obese non-diabetic children and adolescents.

METHODS: children and adolescents aged 5-16 years with BMI ≥ 2.0 SDS were recruited. Criteria of exclusion from the study were pre-term or post-term birth, genetic or endocrine causes of obesity, chronic diseases, or chronic pharmacological therapies. All the patients underwent clinical and biochemical assessment, including oral glucose tolerance test (OGTT), liver ultrasonography (US), and measurement of serum and fecal zonulin levels. Homeostasis model assessment of insulin resistance (HOMA-IR), β-cell function (HOMA-B), Matsuda-index, Insulinogenic-index (IGI), areas under the curves for glucose and insulin were calculated. IR was defined as HOMA-IR >2.5 in prepubertal children and >4 in pubertal youths.

RESULTS: 78 obese patients were enrolled (mean age 11.48 ± 2.54 years). Impaired fasting glucose was documented in 29.5% patients and impaired glucose tolerance in 14.1%. Overall, 69.2% patients had insulin resistance. Liver steatosis was diagnosed in 39.7%. Median serum and faecal zonulin levels were respectively 14.66 ng/ml (range 12.64-19.62) and 76.18 ng/ml (range 46.60-105.44). Serum and faecal zonulin were positively correlated (p=0.03). Moreover, a positive association between serum and faecal zonulin (OR 0.153;95%CI,0.015-0.291;p=0.031) was documented by linear regression model. No significant differences in serum and faecal zonulin levels were found for age, sex, pubertal status, glucose, lipid profile and the other obesity-related parameters. An inverse relationship between faecal zonulin and IGI (OR-0.254; 95%CI,-0.106-0.007;p=0.025) was documented by linear regression analysis and confirmed by the multivariate model (p<0.05), independently from sex, age, BMI, pubertal status, HOMA-B and steatosis. A negative association between faecal zonulin and HOMA-B was also recorded, although this finding did not reach statistical significance (p=0.07).

CONCLUSIONS: the present study described for the first time serum and faecal zonulin levels in a pediatric cohort with obesity. Our results highlighted a close, negative, association between faecal zonulin and IGI. Insulin sensitivity seems to significantly influence faecal zonulin concentrations in children and adolescents with obesity. Even if further studies are needed, these data may support the role of faecal zonulin as a reliable non-invasive biomarker of IR.

Molecular Stability of Antigen-Specific Regulatory T Cells: Promising Candidates for Type 1 Diabetes Therapy

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Type 1 diabetes (T1D) is a prevalent autoimmune disorder, particularly among children. Current clinical trials are exploring the use of regulatory T cells (Tregs) to extend the survival of β-cells. We developed a method using monocytes presenting T1D-specific antigens (insulin β chain peptide 9-23) to induce the proliferation of antigen-specific Tregs (SPEC Tregs). These SPEC Tregs demonstrated high functional potential. However, producing SPEC Tregs takes longer than generating polyclonal Tregs, making it essential to maintain their molecular and functional characteristics.

In this study, we aimed to compare the molecular status of polyclonal Tregs, SPEC Tregs, and unspecific Tregs (UNSPEC Tregs). We also compared Treg features with the counter-population of CD4+ - T effector cells (Teffs). Using RT-qPCR, we analyzed mRNA levels of a panel of genes. MSP-qPCR was employed to measure the methylation status of promoter regions, TSDR, and exon 2 of FOXP3 and CTLA4, respectively, as these genes play pivotal roles in Treg function. Additionally, we examined global DNA methylation and 21 total histone H3 modifications (ELISA).

Our results revealed a transient decrease in FOXP3 gene expression in SPEC Tregs between days 3-6 of cell culture, associated with a decline in STAT5A. However, FOXP3 expression stabilized during SPEC Treg cell expansion. In SPEC Tregs, a positive correlation was observed between FOXP3, CTLA4, and CREB, and a negative correlation with SATB1 gene expression. At the end of cell culture, the expression of other genes was stable with no significant differences between polyclonal and SPEC Tregs. Compared to SPEC Teffs, all Tregs exhibited higher expression of Treg-related genes except for TNFRSF18 and IKZF4.
SPEC Tregs displayed lower global DNA methylation compared to UNSPEC cells. However, promoters and TSDR of FOXP3 and exon 2 of CTLA4 were highly demethylated across all Treg subsets. When analyzing H3 modifications we saw that polyclonal Tregs exhibited the highest level of all modifications (activating and inactivating), while the lower level was observed in UNSPEC Tregs. Interestingly, in paired Tregs/Teffs, a high level of a particular modification in one subset corresponded with a low level in the other.

In summary, our findings confirm that the manufacturing process of SPEC Tregs does not induce a molecular shift towards effector-like cells but preserve their stable Treg characteristics. However, since monocyte stimulation alters H3 modifications in Teff cells, it is crucial to adhere to stringent Treg sorting protocols to ensure the safety of cell therapy.

The Influence of Combined Therapy with T regulatory cells and Rituximab in Children with Type 1 Diabetes on B cells' Phenotype and antibody profile

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Keywords: type 1 diabetes T regulatory cells, B cells, clinical trial, humoral immune response

Background of the research: In type 1 diabetes (T1D), the underlying mechanism of the disease is an imbalance of autoaggressive T cell responses and impaired immunosuppressive cell function. In recent years, there have been more efforts to introduce disease-modifying strategies, particularly immunotherapy targeting T or B cells, and cell therapy with T regulatory cells (Tregs).

Study Design and Methods: In a clinical trial (ISRCTN37116985), T1D children received either Treg cell therapy (n=13), Treg cell therapy combined with rituximab (a monoclonal antibody anti-CD20) (n=12), or a placebo (control group) (n=11). Over a 2-year follow-up, the phenotype of B and T cells was analyzed from peripheral blood samples using flow cytometry. Additionally, immunoglobulin subclasses and cytokine concentrations were measured in multiplex assays using Luminex technology.

Results: The study revealed significant changes in B cell subsets following rituximab treatment. There was a notable increase in transitional B cells (CD38+CD24+) at the 12- and 24-month follow-up visits, while memory B cells (CD27+) decreased. Interestingly, the proportion of CD38++CD24++ B cells, enriched with regulatory B cells (Bregs), was the highest in the combined treatment group at the 12-month follow-up but over time decreased in the control group and remained stable in the Treg cell therapy-only group. Rituximab treatment also led to a shift in antibody production, decreasing IgG1 in favor of IgG2 antibodies. While anti-insulin antibody concentrations decreased across all groups, anti-GAD specific antibodies were significantly lower in the combined treatment group at the 24-month visit. Treg cell therapy increased the production of immunosuppressive cytokines, and in the combined treatment group, a positive correlation between IL-4 and IL-5 with IgG2 and IgG1, respectively, was observed at 12 months post-treatment.

Conclusion: The implementation of Treg cell therapy with rituximab may improve therapy outcomes by altering the B cell compartment, increasing the proportion of naive, transitional, and Breg-like cells. This leads to the depletion of memory B cells and a decrease in GAD-specific autoantibodies, as well as a switch to the production of antibody subclasses with low complement-binding affinity.

Thyrotropin receptor stimulating antibodies in pediatric patients with Graves' disease using ultra rapid turbo bioassay

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Background: Thyrotropin receptor (TSH-R) stimulating autoantibodies (TSAb) are present in 95-99% of patients with Graves' disease (GD). TSAb are functional, impact thyroid function, and are clinically relevant. This study we performed in pediatric patients with dynamic of Graves' disease before and during methimazole therapy and in a patient with Hashimoto's thyroiditis (HT) using a novel and ultra-rapid TSAb bioassay.

Methods: All samples from patients with autoimmune thyroid disease (AITD) and healthy controls were tested at the accredited and certified academic thyroid lab of the JGU Medical Center (Mainz, Germany) with a new "TurboTM" TSAb bioassay (Thyretain®, Quidel) with a readout that is based on a cyclic AMP-activated luciferase. The negative values for anti-thyroid receptor antibodies were: < 0,024 IU/L Results: Median age was 12 years (patients n=80 / healthy controls n=35; 12/10.5 years) and female: male ratio was 1,65. Of 80 samples, 43 (52.5%), 30 (36,5%) and 7 (11%) were hyperthyroid, hypothyroid and euthyroid respectively. The TSH-R-Ab assays were negative in 35 healthy controls devoid of autoimmune thyroid and endocrine disorders. Of 80, selected pediatric AITD patients (GD and HT), 41 were positive for TSAb. In the TurboTM cAMP TSAb assay was detected TSAb in 36 untreated GD patients (100%) and 5 treated by methimazole samples. The TurboTM TSAb bioassay highly correlated with thyroid function (p=0.028). Three of 80 (3.75%) samples showed dual TSH-R-Ab positivity.

Conclusions: This is the largest reported collective of TSAb-positive samples in pediatric Graves' disease, measured by a rapid and reliable "TurboTM" TSAb bioassay. TSAb markedly affects thyroid function. Furthermore, the novel TurboTM stimulating bioassay is clinically useful in the monitoring of pediatric Graves' patients.

Assessment of regulatory B cells in peripheral blood and zinc transporter 8 expression in thyroid tissue in children with autoimmune thyroid diseases

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Introduction: There has been a growing trend in the incidence of autoimmune thyroid diseases (ATD) in the pediatric group of patients. The new aspects of its pathogenesis may contribute to understand innovative methods of prevention and treatment. Regulatory B cells (Breg) allow the maintenance of immune homeostasis by neutralizing the negative reactions of effector cells. Attention has been recently paid also to the new environmental factor like zinc and its receptor- ZnT8, that may have properties to support the functionality of T and B cells.

Aim: The aim of this study was to assess the percentage of Breg with the specific phenotypes in children with ATD, to evaluate the effect of treatment on the percentage of Breg and effector cells and to assess the ZnT8 expression in thyroid tissue in patients after thyroidectomy due to Graves' disease (GD).

Material and methods: The study consisted of 3 different research groups: the first with 53 patients with ATD (12- GD and 10 with Hashimoto's thyroiditis- HT) and 15 healthy control, the second group consisted of 17 patients with non-toxic nodular goitre (NTNG) and 20 with GD after thyroidectomy and the third consisted of 22 GD patients treated with methimazole, compared to 31 healthy control. Cells were analyzed using a BD FACS Calibur cytometer and FlowJo software. The obtained data were processed using the statistical software GraphPad Prism 5.0 and Statistica 12.0. ZnT8 expression in human thyroid tissues was investigated by simultaneous immunohistochemical, Western Blot and immunofluorescence analyses.

Results: There was a decrease in IL-10 production by Breg cells expressing CD19+CD24+CD27+IL-10 and CD1d+CD5+CD19+IL-10+ in both untreated and treated ATD patients. Significantly higher levels of Th1, Th17 and Th22 effector cells were found in patients with GD. Thiamazole did not significantly affect the changes within the examined cells. Patients with GD showed significant correlations between Breg and Th1 and Th17 cells. Expression of the ZnT8 transporter was identified by immunohistochemistry in thyroid tissues of patients with GD and NTNG. This expression was found in follicular and C cells by fluorescence method.

Conclusions: The reduction in the level of Breg lymphocytes with the CD19+CD24+CD27+IL-10+ and CD19+IL-10 phenotype may be responsible for the violation of immune tolerance in the course of GD. The presence of ZnT8 expression in the thyroid tissue of patients with GD may suggest the potential role of this transporter as another autoantigen.

The infalliability of newborn screening tests - a case of a 3-month-old boy with congenital adrenal hyperplasia

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Keywords: congenital adrenal hyperplasia (CAH); children; newborns; screening test

Background of the research: Congenital adrenal hyperplasia (CAH) is a disease that belongs to the group of autosomal recessive inherited disorders, caused by mutations in genes encoding enzymes that lead to biochemical stages of producing glucocorticoids, mineralocorticoids, or sex steroids from cholesterol by the adrenal glands. Most of these diseases are associated with excessive or insufficient production of sex hormones, which can affect the development of primary or secondary sexual characteristics in some affected infants, children, and adults. Furthermore, insufficient production of mineralocorticoids can lead to severe salt loss, increasing neonatal morbidity and mortality. The greatest challenge in treating CAH is avoiding excessive treatment with glucocorticosteroids and controlling the imbalance of sex hormones. An accurate diagnosis is also crucial as there is a new path for treatment of CAH - a gene therapy - which expands the possibilities and gives a chance to improve lives of many patients.

Methods: A 3-month-old boy was referred to the Clinic of Pediatrics, Endocrinology, Diabetology with the Cardiology Divisions due to elevated levels of 17-OH Progesterone and abnormal, darker pigmentation of the scrotum. Screening tests, performed from a blood spot sample, ruled out metabolic diseases, including congenital adrenal hyperplasia. Additionally, a physical examination revealed signs of upper respiratory tract infection. Laboratory tests showed normal cortisol and ACTH levels.

Results: During a following hospitalisation, a 24-hour urine collection was conducted to determine the steroid profile, which revealed significantly elevated excretion of androgen metabolites, 17-OHP, and 21-deoxycortisol. The steroid profile, despite negative screening tests, confirmed the diagnosis of CAH caused by 21-hydroxylase deficiency.

Conclusions: Congenital adrenal hyperplasia results in numerous long-term complications, causing abnormal growth and development or infertility, and requires continuous medication. Universal newborn screening for metabolic diseases, conducted in Poland and other developed countries, is essential for early diagnosis and the initiation of appropriate therapy. Despite this, we must remain vigilant during the examination of pediatric patients and the search for relevant symptoms, regardless of laboratory results.

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